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RESEARCH ARTICLE

# CREST Syndrome

**Yulia Varavko[1,*], Artem Slautin[2]**

[1]*Associate Professor of the Department of Propaedeutic of Internal Diseases, Federal State Budgetary Educational Institution of Higher Education "Irkutsk State Medical University" of the Ministry of Health of the Russian Federation, Irkutsk, Russia*

[2]*resident in the specialty of therapy, Federal State Budgetary Educational Institution of Higher Education "Irkutsk State Medical University" of the Ministry of Health of the Russian Federation, Irkutsk, Russia*

[*]**Corresponding Author**: Yulia Varavko, Associate Professor of the Department of Propaedeutic of Internal Diseases, Federal State Budgetary Educational Institution of Higher Education "Irkutsk State Medical University" of the Ministry of Health of the Russian Federation, Irkutsk, Russia, Tel.: +79025780497, E-mail: roza1983@mail.ru

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## Abstract

Dedicated to modern data on the clinical manifestations, diagnosis and treatment of CREST syndrome - a variant of systemic scleroderma.

**Methods**: based on an analysis of publications devoted to the study of pathogenetic mechanisms, diagnostic features and approaches to treatment of CREST syndrome.

**Results**: CREST syndrome is characterized by damage to the skin, blood vessels and internal organs, manifested by calcification, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia; the development of the disease is based on disorders of the immune system and vascular dysfunction. Diagnosis is based on the assessment of clinical, laboratory and instrumental data; treatment includes symptomatic and pathogenetic therapy aimed at correcting immune and vascular disorders. Particular attention is paid to interstitial lung disease (ILD) as one of the most serious complications, occurring in 35-52% of patients.

**Keywords:** CREST Syndrome; Systemic Scleroderma; Autoantibodies; Vascular Dysfunction; Calcification; Raynaud's Phenomenon; Esophageal Dysfunction; Diagnosis; Treatment; Prognosis

## Introduction

CREST-syndrome is a limited form of systemic scleroderma, characterized by damage to the skin and internal organs. This is an acronym made up of the first letters of the main manifestations: calcification, Raynaud's phenomenon, esophagitis, sclerodactyly and telangiectasia [1, 5].

One of the most serious complications CREST- syndrome is interstitial lung disease (ILD). ILD found in 35-52% patients with systemic scleroderma and is responsible for 20-40% of deaths [5].

Vascular disorders play a key role in the pathogenesis of systemic scleroderma, including CREST- syndrome. There are three main phenotypes of vascular lesions: small vessel lesions (Raynaud's phenomenon, telangiectasia, digital ulcers), macroangiopathy (atherosclerosis, vascular calcification) and pulmonary artery lesions (pulmonary arterial hypertension).

Raynaud's phenomenon is one of the earliest and most common manifestations of systemic scleroderma, occurring in 90-98% of patients, it is characterized by episodic circulatory disorders in the distal extremities due to vasospasm of small arteries and arterioles [1].

Pulmonary arterial hypertension develops in approximately 10-15% of patients with systemic scleroderma and is associated with a poor prognosis. PAH is more common in the limited form than in the diffuse form [1, 5].

CREST- syndrome generally characterized by a more favorable course compared to other forms of systemic scleroderma; some patients may develop severe complications, such as pulmonary hypertension and damage to internal organs.

One of the pathogenetic mechanisms CREST- syndrome is an autoimmune process leading to the production of specific autoantibodies, patients with CREST- syndrome characterized by high titers of antinuclear antibodies, including antibodies to centromeres and topoisomerase.

These autoantibodies cause damage to the vascular endothelium, which leads to disruption of microcirculation and the development of symptoms such as Raynaud's phenomenon and telangiectasia. Endothelial dysfunction contributes to fibrosis of target organs, including the skin, esophagus and other internal organs.

Along with autoimmune disorders, in the pathogenesis CREST- syndrome vascular dysfunction is important: damage to the vascular endothelium leads to impaired vasodilation, increased vascular permeability and activation of fibrosis processes [1, 2, 4]. Changes underlie the development of such symptoms CREST- syndrome, as a Raynaud's phenomenon, telangiectasia and cutaneous calcification, vascular dysfunction contributes to damage to internal organs, including the lungs, kidneys and heart [1, 4].

Immune disorders lead to damage to the vascular endothelium and activation of fibrosis processes, this triggers a cascade of pathological changes characteristic of this disease [1, 4].

Acronym CREST composed of the first letters of the five main clinical symptoms of this form of the disease: calcinosis, Raynaud's phenomenon, Esophageal dysfunction, sclerodactyly and telangiectasias [2, 5].

Calcinosis and subcutaneous tissue is one of the most characteristic manifestations CREST- syndrome, it is manifested by the formation of dense subcutaneous deposits of calcium salts, which can be localized on the skin of the fingers, hands, forearms, elbows, knees and feet [2, 4]. These calcifications can cause pain, skin ulceration and recurrent infections [2].

Raynaud's phenomenon – this is a spasm of small blood vessels, mainly of the fingers and toes, less often of the nose, ears and tongue, it is manifested by a characteristic three-phase change in skin color: pallor, cyanosis and hyperemia [2, 4, 5]. This symptom occurs in almost all patients with CREST- syndrome and may be one of the first manifestations of the disease [2, 4].

Esophageal dysfunction, damage to the esophagus in the CREST- syndrome manifested by a violation of its motor function, which leads to the development of reflux esophagitis, dysphagia and dyskinesia of the lower third of the esophagus. This complication occurs in more than 80% of patients with CREST- syndrome [2, 5].

Sclerodactyly characterized by thickening and thinning of the skin of the fingers, which leads to limited mobility. This symptom is observed in almost all patients with CREST- syndrome.

Telangiectasias are dilated capillaries that are visualized on the skin in the form of small red spots. They are most often localized on the face, neck, chest and upper extremities [2, 4].

CREST- syndrome characterized by damage to the skin, blood vessels and internal organs, manifested by calcification, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasias, the incidence of these symptoms varies from 60% to 100% in patients with this form of systemic scleroderma [2].

Diagnostics CREST- syndrome is based on a comprehensive assessment of clinical symptoms, laboratory parameters and results of instrumental studies.

The elements of the diagnostic algorithm are the main diagnostic criteria:

- Anamnesis and physical examination, identification of characteristic clinical manifestations: calcification of the skin, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia;
- Laboratory studies, determination of antinuclear antibodies, including antibodies to centromeres and topoisomerase.
- Assessment of inflammatory markers (ESR, C-reactive protein), examination of respiratory function, cardiovascular system, kidneys and liver.
- Instrumental methods, video capillaroscopy of the nail bed to detect microangiopathy.
- Chest X-ray or CT to evaluate interstitial lung disease.
- Esophagogastroduodenoscopy to diagnose esophageal lesions.
- Ultrasound examination of the heart to detect pulmonary hypertension.

Management of patients with CREST- syndrome includes both symptomatic therapy aimed at relieving individual manifestations of the disease, and pathogenetic treatment affecting the basic mechanisms of disease development.

For severe skin calcification, bisphosphonates, colchicine, and surgical excision of calcifications are used. Prokinetic drugs and proton pump inhibitors are used to treat esophageal dysfunction. Interstitial lung disease (ILD) is one of the most common and serious manifestations of systemic scleroderma (SSc). It occurs in approximately 35-52% of patients with SSc and is responsible for 20-40% of deaths. In a review published in The Lancet Respiratory Medicine, Perelas and co-authors review in detail the epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment of IPL in SSc. [5].

Systemic scleroderma is an insidious autoimmune disease that affects not only the skin, but also internal organs. One of its most dangerous manifestations is interstitial lung disease (ILD). IPL occurs in every third or second patient with systemic scleroderma. It most often affects African Americans and those diagnosed with the diffuse form of the disease or with antibodies to topoisomerase 1.

The pathogenesis is based on a fatal triumvirate: vascular disorders, autoimmune inflammation and uncontrolled fibrosis of the lung tissue. Damage to the vascular endothelium triggers a chain reaction - fibroblasts are activated, extracellular matrix is deposited, and the lungs gradually turn into dense connective tissue.

At first, the symptoms of IPD may be subtle - shortness of breath on exertion, dry cough. But over time, the disease progresses, breathing becomes more and more difficult. High-resolution computed tomography reveals a characteristic lesion pattern - nonspecific interstitial pneumonia.

Diagnosis of IPD requires a multidisciplinary approach - the rheumatologist, pulmonologist and radiologist must work in close collaboration. Pulmonary function tests and blood gas tests help assess the extent of the damage.

Treatment is aimed at suppressing autoimmune inflammation and fibrosis. Immunosuppressive drugs such as mycophenolate mofetil and cyclophosphamide are the standard for inducing remission. Doctors also have antifibrotic drugs in their arsenal - nintedanib and pirfenidone. And in the most severe, refractory cases, a lung transplant may be required.

Table 1 provides a comprehensive overview of the main aspects CREST- syndrome, it contains information about the mechanisms of disease development, the frequency of detection of major autoantibodies, clinical manifestations, diagnostic criteria and treatment methods.

**Table 1:** Review of mechanisms, clinical manifestations, diagnostic criteria and treatment methods CREST-syndrome

| Name | Description |
|---|---|
| Mechanism | - Activation of autoreactive T cells- Production of autoantibodies to various components of connective tissue- Damage to vascular endothelial cells |
| Vascular changes | - Spasm and obliteration of small vessels- Impaired microcirculation and tissue hypoxia- Activation of fibrosis processes |
| Fibrosis of tissues | - Excessive accumulation of collagen and other extracellular matrix components- Transformation of fibroblasts into myofibroblasts- Imbalance between collagen synthesis and degradation |
| Genetic predisposition | - Polymorphism of genes regulating the immune response and fibrosis- Epigenetic changes |
| Frequency of detection of major autoantibodies in CREST-syndrome | |
| Autoantibody | Detection rate, % |
| Antibodies to centromeres | 80-90 |
| Antibodies to topoisomerase I | 10-20 |
| Frequency of main clinical manifestations CREST-syndrome | |
| Symptom | Frequency, % |

| | |
|---|---|
| Raynaud's phenomenon | 90-100 |
| Sclerodactyly | 90-100 |
| Telangiectasia | 70-80 |
| Esophageal dysfunction | 80-90 |
| Calcinosis | 60-70 |
| Basic diagnostic criteria CREST-syndrome | |
| Criterion | Description |
| Calcinosis | Presence of dense subcutaneous deposits of calcium salts |
| Raynaud's phenomenon | Characteristic three-phase discoloration of the skin of the fingers |
| Esophageal dysfunction | Dysfunction of the lower third of the esophagus |
| Sclerodactyly | Thickening and thinning of the skin of the fingers |
| Telangiectasia | Dilated capillaries on the skin |
| Antibodies to centromeres | High titers of antinuclear antibodies |
| Basic treatment methods CREST-syndrome | |
| Symptom | Treatment methods |
| Raynaud's phenomenon | Calcium channel blockers, inhibitors Phosphodiesterase -5, prostacyclins |
| Calcinosis | Bisphosphonates, colchicine, surgical excision |
| Esophageal dysfunction | Prokinetic drugs, proton pump inhibitors |
| Pathogenetic therapy | Rituximab, inhibitors Phosphodiesterase -5, guanylate cyclase stimulators |

Treatment for scleroderma is aimed at controlling symptoms and slowing the progression of the disease. Recommended:

- use of topical corticosteroid creams and ointments to reduce inflammation and swelling of the skin;
- taking immunosuppressive drugs such as methotrexate or mycophenolate mofetil to suppress the autoimmune reaction;
- use of vasodilators (for example, calcium channel blockers) to improve blood circulation and prevent the development of complications from internal organs;
- physiotherapy and exercise therapy to maintain joint and muscle mobility;
- regular monitoring of the condition of internal organs using X-rays, ECG, spirometry and other methods.

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